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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/308,150	09/30/1999	WALTHERUS JACOBUS W VAN VENROOIJ	30394-1027	5796

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PEACOCK MYERS AND ADAMS P C
P O BOX 26927
ALBUQUERQUE, NM 871256927

EXAMINER
DECLOUX, AMY M

ART UNIT	PAPER NUMBER
1644	23

DATE MAILED: 07/29/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/308,150	Applicant(s) VAN VENROOIJ ET AL.	
	Examiner Amy M. DeCloux	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2002 and 13 February 2002 and 25* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-9 and 15-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-9 and 15-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 1-25-02, Paper No. 19, for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/308,150, is acceptable and a CPA has been established. An action on the CPA follows.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1, 3-4, 7-9 and 17-24 and the sequence of SEQ ID NO:10 and citrulline as species in Paper No. 22, filed 5-9-02, is acknowledged. The traversal is on the ground(s) that under MPEP 819 the previous express election carries forward. This is not found persuasive because as pointed out by Applicant, the instant application has been filed as a divisional and therefore under MPEP 819 a restriction is proper. Applicant further points out that the restriction is improper because claim 21 recites a cyclic peptide and accordingly should have been placed in Group II as well as Group I with which the examiner agrees. Upon reconsideration Groups I and II and III have been rejoined.

The requirement is still deemed proper and is therefore made FINAL.

Priority

3. It is noted that the translation of the foreign priority document indicates that said document does not contain SEQ ID NO:s 4-10, therefore claims 4-6 and 21-24 are accorded the filing date of 11-14-1997.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

5. Claims 1, 3-4, 8 and 17-22 and 24 are rejected under 35 U.S.C. 101 because, the claimed invention is directed to non-statutory subject matter. A peptide recited in the instant claims would read on naturally occurring peptides in an arthritic patient and thus would be a composition of nature and constitutes non-statutory subject matter. Modifying the word peptide with the adjective purified or isolated would overcome this rejection.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-9 and 15-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

In the instant case, the specification does not convey to the artisan that the applicant had possession, at the time of invention, of the claimed peptides (with the exception of the peptides consisting of the sequence disclosed in Table 1 of the specification). Due to this broad definition of a peptide derived from any antigen recognized by any autoantibodies from patients with rheumatoid arthritis , none of these peptides (with the exception of the peptides consisting of the sequence disclosed in Table 1) meets the written description provision of 35 USC 112, first paragraph. Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See Vas-Cath, page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath, page 1116.).

The skilled artisan cannot envision all the contemplated peptides that are derived from any antigen recognized by any autoantibodies from patients with rheumatoid arthritis, even those with a formula according Formula I as recited in claim 2 and therefore conception cannot be not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

The open language of claims 1-9, 15-24, such as the term comprising recited in claims 4, 6 and 18, and the phrase "A peptide of about 21 or fewer amino acids" as recited in line 1 of claim 1 and also in line 1 of claim 17, and of the phrase "A peptide with an amino acid sequence" as recited in line 1 of claim 21, means the peptide can also encompass an indeterminate number and type of additional amino acids, in addition to the amino acids in the recited SEQ ID NO:s. Given the indefiniteness of the additional amino acids that may be encompassed in the polypeptide and the methods thereof, the instant claims are not adequately described, given that the prior art does not provide compensatory structural or correlative teachings to enable one of skill to identify a polypeptide encompassed by the method recited in said claims along the lines of reasoning discussed in the previous paragraphs.

Therefore, only the peptides of Table 1 but not the full breadth of the instant claims, meets the written description provision of 35 USC 112, first paragraph. Applicant is reminded

that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.) Applicants are directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 64, No. 244, pages 71427-71440, Tuesday December 21, 1999.

Note: The examiner disagrees with applicant's statement in the remarks section of the response to final rejection mailed 2-13-02 Paper No. 20, that claims 4 and 6 are not rejected under 112 first written description, due to the open language of comprising. Applicants traverse the rejection on the grounds that a large genus is not a proper basis for a written description rejection. Although the instant claims recite a peptide and a method comprising said peptides, and not a cDNA, the same principle applies; A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly&Co.*, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997. Therefore, the written description guidelines indicate that the instant specification must describe the boundaries of the genus. In the instant application the genus that applicant has described consists of only peptides derived from two areas of one protein which contain one type of arginine modification (citrulinne).

8. Claims 1, 3-9 and 15-24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a peptide from Table 1 , consisting of SEQ ID NO:s 1-9, and a cyclic peptide consisting of SEQ ID NO:10, and method thereof, does not reasonably provide enablement for any peptide from any antigen recognized by autoantibodies from patients with rheumatoid arthritis as recited in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention with any peptide other than those peptides consisting of SEQ ID NO:s 1-10 without an undue amount of experimentation. Other than the sequences of SEQ ID NO:1-10, the specification has not provided any biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies a) any peptides from any antigen wherein said peptide contains any modified arginine residue other than citrulline, or wherein said peptide is any peptidic fragment of profilaggrin, or wherein said peptide may be cyclized by any way other than through cysteine residues, and wherein said peptide reacts with autoantibodies from a patient with rheumatoid arthritis as recited in the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most clearly connected, to make any of the recited peptides with the exception of peptides consisting of SEQ ID NO:s 1-10, wherein said peptide would be reactive with autoimmune antibodies from a patient with rheumatoid arthritis, nor to use any of said peptides with the exception of peptides consisting of SEQ ID NO:s 1-10 in a method for the detection of autoimmune antibodies as recited in claim 15, commensurate in scope with these claims.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth.

There is insufficient guidance in the instant specification to predict which sequence modifications of arginine in which peptides in which antigens will retain the ability to be reactive with autoimmune antibodies from a patient with rheumatoid arthritis. Predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functions and properties requires a knowledge of, and guidance with regard to which amino acids in the sequence, if any, are tolerant of modification and which are conserved or less tolerant to modification, and detailed knowledge of the ways in which the product's structure relates to its functional usefulness. differences effects the ability of said polypeptides to bind to an autoantibody, which would lead to undue experimentation, especially in view of the teachings of Abaza et al (J. Of Protein Chemistry, 11(5):433-444, 1992). Abaza et al show that even a single amino acid difference in an antigen may effect antibody binding by teaching that an amino acid substitution of myoglobin outside the epitope recognized by a monoclonal antibody causes the myoglobin to be unreactive with said antibody, (see entire article, especially the Abstract). Therefore predicting which peptides and modifications thereof, will retain the ability to bind autoantibodies in a patient with rheumatoid arthritis as recited in the instant claims , with the exception of SEQ ID NO:s 1-10, and therefore which peptides will be useful in a method of detection of autoimmune antibodies as recited in claim 15, is complex and well outside the realm of routine experimentation. In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and this is not sanctioned by the statute.

Note: Applicant traverses the rejection on the grounds that the amendment to claim 1 should overcome the rejection. However, it is noted that claim 1 has not been instantly amended.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 3-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 and dependent claims 3-16, claim 17 and dependent claims 18-20, and claim 21 and dependent claims 22-24, are indefinite in their recitation of the phrase "A peptide of about 21 or fewer amino acids" as recited in line 1 of claim 1 and also in line 1 of claim 17, and of the phrase "A peptide with an amino acid sequence" as recited in line 1 of claim 21, because it is not clear if said phrases are closed or open language. The phrase "consisting off" or "set forth" can be used for closed language, while "comprising" or "having" is considered open.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) do not apply to the examination of this application as the application being examined was not (1) filed on or after November 29, 2000, or (2) voluntarily published under 35 U.S.C. 122(b). Therefore, this application is examined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

12. Claims 4 and 21-24 are rejected under 35 U.S.C. 102(a) as being anticipated by Schellekens et al. (Arthritis and Rheumatism Vol. 40, No. 9 suppl. 8-12 November 1997)(in IDS)

Schellekens et al. teach synthetic peptides derived from an antigen that contains a modified arginine, specifically the modified arginine residue citrulline, and that they are reactive to antibodies specifically present in rheumatoid arthritis sera directed against filaggrin (see entire abstract). Schellekens et al. teach also that a method of detecting said antibodies could be detected in the in rheumatoid arthritis sera with an ELISA assay. Therefore, the referenced teachings anticipate the claimed invention. The claims are included in the rejection due to their open language. Closed language would overcome this rejection.

13. Claims 1, 3-4, 8, 21-22 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Simon et al J. Clin. Invest. 92:11387-1393, 1993,(IDS), as evidenced by WO/ 99/35167.

Simon et al teach that filaggrin is recognized by auto-antibodies specifically in RA patients (see Abstract and page 1387, column 2, last sentence of second paragraph.). Therefore, the referenced teachings anticipate the claimed references. It is noted that even though the modification of Arginine was not taught, the claimed functional limitations would be inherent properties of the referenced peptides, as evidenced by WO/99/35167. '167 teaches that citrulline

containing peptides of human filaggrin reacted with autoantibodies of rheumatoid arthritis (see entire article, especially the Abstract).

Note the open language indicated by the term "with" in line 1 of claim 21. Also note that post filing date references can be used in support of inherent features taught in the primary 102 reference.
Also note The office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the Factor V deficient plasma of the prior art and the instant application. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed modifications of filaggrin are different from those taught by the prior art and to establish patentable differences. (See In re Best 562 F.2d 1252 195 USPQ 430 (CCPA) and Ex parte Gray 10 USPQ 2d 1922 (PT) Bd. Pat App. & Int, 1989).

Note: Applicant states that by amending claim 21 by changing the open language "having" the rejection is overcome. However, as discussed in the 112 second paragraph rejection, it is not clear if the substituted phrase is open or closed.

14. Claims 1, 3-4, 7-9, 15-24 rejected under 35 U.S.C. 102(e) as being anticipated by Serre et al. US Patent 5,888,833 Issued 3-30-1999, filed 6-3-1994.
'883 teaches a peptides of fewer than 21 amino acids reactive with autoimmune antibodies from a patient suffering from RA comprising a modified arginine residue of citrulline in profilaggrin or filaggrin or fragments thereof, including synthetic fragments, a method for detection of human autoimmune antibodies in sera comprising contacting said peptide with said sera , see entire patent, especially the abstract, column 4, lines 30-67, columns 5-8, column 9, lines 35-60. Therefore, the referenced patent anticipates the claimed invention.

15. No Claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy M. DeCloux whose telephone number is 703 306-5821. The examiner can normally be reached on M-F 8:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 703 308-3973. The fax phone numbers for the organization where this application or proceeding is assigned are 703 305-3014 for regular communications and 703 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 308-0196.

Amy DeCloux, PhD,
Patent Examiner, Group 1640
July 26, 2002
Amy DeCloux
7-26-02